tylcyclohexanecarboxylic acid. A mixture of cis[29] and trans[29] nitriles was prepared from the acid by successive conversion to the acid chloride (PCl_5) and the amide (aqueous NH_3) followed by dehydration ($POCl_3$). The isomers were separated by preparative GLC (30% Carbowax 20M).

(29) N. L. Allinger and W. Szkrybalo, *J. Org. Chem.*, **27**, 4601 (1962).

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Registry No. 1, 15619-19-9; 2, 15619-18-8; 4-*tert*-butylbenzoic acid, 98-73-7.

Chlorination of Aliphatic Ketones in Methanol

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The chlorination of aliphatic ketones in methanol has been examined. The product distributions in methanol differ substantially from those obtained by chlorination in carbon tetrachloride. The reaction in methanol favors addition of chlorine to the least substituted carbon α to the carbonyl group. The effect is especially pronounced if an α carbon bearing two substituents is present. The distribution of products is determined by the relative stability of the enol ethers formed from the ketone under the reaction conditions.

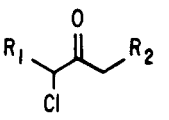
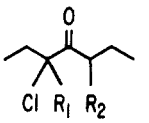
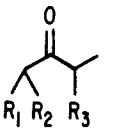
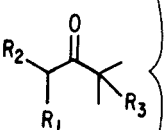
The monobromination of various ketones in the presence of methanol has been reported to give substantially different product distributions vs. bromination in other solvents.[1,2] Exclusive α,α'-halogenation has been observed when cyclic ketones or their ketals are brominated in methanol.[3] It was of interest to determine if the effect of methanol on the orientation of halogenation in these systems extended to the halogenation of aliphatic ketones. In addition to exploring the effects of the ketone structure and solvent on the regiospecificity of halogenation, the type of halogen used in this reaction is also an important variable. While both α-bromo and α-chloro ketones are reported to undergo acid-catalyzed rearrangement, α-bromo ketone equilibration has been more readily observed.[4,5]

Results

Methanol solutions of acetone, 2-butanone, 3-methyl-2-butanone, or 4-heptanone were allowed to react with 1 or 2 equiv of chlorine at 20–50 °C. Chlorine is bubbled into the reaction mixture. After a short induction period, the yellow solution becomes colorless and the temperature increases. When addition of 1 equiv of chlorine is complete, the solution turns yellow and cooling of the reaction is necessary. The reaction products at this point are HCl and a mixture of monochloro ketones and their dimethyl ketals. Addition of a second equivalent of chlorine at room temperature leads to further chlorination. The final products are mixtures of dichloro ketones and their ketals (Table I). At room temperature further chlorination, even with excess chlorine present, is slow.

For the purpose of comparison, the same set of ketones listed above was allowed to react with 1 or 2 equiv of chlorine in carbon tetrachloride. The results are also summarized in Table I.

Table I. Ketone Chlorination Products[a]

		R_1=Cl	R_2=H	R_2=Cl	R_1=H
	MeOH	-	(40)	-	(60)
	CCl_4	67		33	
		R_1=Cl	R_2=H	R_2=Cl	R_1=H
	MeOH	7	(-)	44	(49)
	CCl_4	41		59	
		R_2R_3=H	R_1=Cl	R_1R_2=H	R_3=Cl
	MeOH	25	(30)	32	(13)
	CCl_4	22		78	
		R_1R_2=Cl	R_3=H	R_2R_3=Cl	R_1=H
	MeOH	16	(3)	22	(59)
	CCl_4	13		87	
		R_1R_2=H	R_3=Cl	R_2R_3=H	R_1=Cl
	MeOH	8	(-)	92	(-)
	CCl_4	53		47	
		R_1R_2=Cl	R_3=H	R_2R_3=Cl	R_1=H
	MeOH	46	(31)	10	(13)
	CCl_4	12		88	

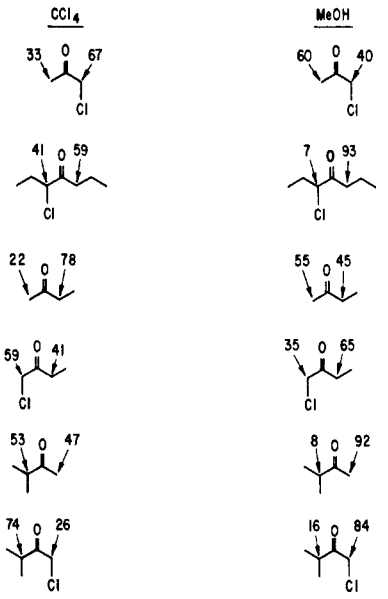
[a] Values in parentheses indicate corresponding dimethyl ketal; dash indicates product not observed.

The reaction mixtures were examined by using gas chromatography. Compounds were identified by mass spectroscopy and coinjection with authentic samples. The isolated yields of chlorination products were good

(1) M. Gaudry and A. Marquet, *Tetrahedron*, **26**, 5611, 5617 (1970).
(2) Y. Jasor, M. Gaudry, and A. Marquet, *Bull. Soc. Chim. Fr.*, 2732, 2735 (1973).
(3) E. W. Garbisch, *J. Org. Chem.*, **30**, 2109 (1965).
(4) M. D. Metha, D. Miller, and D. J. D. Tidy, *J. Chem. Soc.*, 4614 (1963).
(5) E. Warnhoff, M. Rampersad, P. Sundara Raman, and F. W. Yerhoff, *Tetrahedron Lett.*, 1659 (1978).

0022-3263/81/1946-2532$01.25/0

Scheme I. Position of Chlorine Substitution



(80–100%). Chlorinations in methanol were especially clean with only very small amounts of side products (~ 1%). The chlorinations in carbon tetrachloride were also reasonably free of byproducts if temperatures were kept low (<40 °C). If low temperatures were not maintained, especially in the reactions of 2 equiv of chlorine with 4-heptanone or 3-methyl-2-butanone, further reaction of the products was observed. In all of the chlorinations studied, no interconversion of products was detected under the reaction conditions.

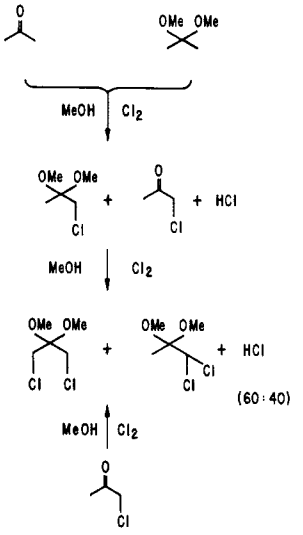
As can be seen by comparing the distribution of reaction products in Table I, the effect of methanol on the orientation of chlorination is substantial. In some cases reaction in methanol gives high selectivity where none is observed in the carbon tetrachloride chlorination. In other cases the preferred position of attack is reversed by changing solvents. The magnitude of the effect methanol has on the product distribution depends strongly on the ketone structure (vide infra).

The regiospecificity of α-chlorination of the ketones investigated is summarized in Scheme I. The position of initial chlorination was determined by a straightforward analysis of the reaction products. In order to determine the chlorination products resulting from addition of a second chlorine, the crude reaction products of the first chlorination were further reacted without isolation. In the case of acetone or 4-heptanone, initial chlorination gives one product; further chlorination occurs to give products as shown in Scheme I. Initial chlorination of 2-butanone or 3-methyl-2-butanone yields a mixture of α-chloro products. Further chlorination of these mixtures gives the product yields shown inTable I.

The regiospecificity of the chlorination of 1-chloro-2-butanone or 1-chloro-3-methyl-2-butanone (Scheme I) is corrected for the dichloro products formed from the other monochloro product present in the initial reaction mixture. In the case of 2-butanone, the 3-chloro isomer initially formed gives only 1,3-dichloro product (3,3-dichloro-2-butanone or its ketal is not observed). The regiospecificity of chlorination of the 1-chloro isomer is corrected for the 1,3-dichloro product formed from the 3-chloro isomer (complete conversion of the 3-chloro isomer to the 1,3-dichloro isomer is assumed).

Similarly the initial chlorination of 3-methyl-2-butanone gives the 1-chloro and 3-chloro isomers. The 3-chloro isomer can yield only 1,3-dichloro products. 1-Chloro-3-methyl-2-butanone gives both 1,1- and 1,3-dichloro products. Assuming quantitative conversion of the 3-chloro isomer to the 1,3-dichloro isomer, the amount of 1,3-dichloro products arising from the 1-chloro isomer is the difference between the total amount of 1,3-dichloro products and the initial amount of 3-chloro isomer present.

Scheme II



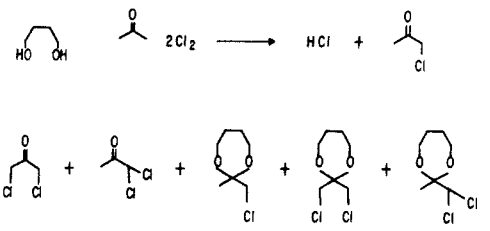
In order to further explore the effect of solvent, the chlorination of acetone (Scheme II) was investigated in detail. Acetone chlorinations were conducted between 10 and 50 °C with no significant change in product distribution. After chlorination the product distribution is unaffected by heating the crude reaction mixture to reflux, or by allowing it to stir at room temperature for several hours. At 0 °C the chlorination of acetone in anhydrous methanol was very slow.

After addition of slightly more than 1 equiv of chlorine to a methanol solution of acetone, chloroacetone dimethyl ketal is the major product. Dichloroacetone dimethyl ketals are minor products and are present in the same ratio as they are after addition of another equivalent of chlorine to the reaction. Addition of HCl or $HClO_4$ at the start of chlorination in methanol, or brief irradiation with a sunlamp, shortened the induction period at the beginning of the reaction but had no effect on the final product distribution. A trace of iodine added to the reaction before chlorination also had no effect on product distribution. Under anhydrous conditions acetone chlorination in methanol yields a 60:40 mixture of the 1,3- and 1,1-dichloroacetone dimethyl ketals. Addition of a small amount of water at the start of chlorination had little effect on the ratio of dichloro ketals. However, dichloro ketones were also observed in the product mixture. The amounts of 1,1- and 1,3-dichloroacetones present varied with reaction conditions to some extent. However, the overall ratio of 1,1- to 1,3-dichlorinated products was constant (60:40). In all cases the ketals were the major products.

The chlorination of 2,2-dimethoxypropane in methanol gave the same results as an analogous reaction starting with acetone. The chlorination of chloroacetone in methanol gave a mixture of dichloro ketals and ketones. The ratio of 1,1- to 1,3-dichloro products was very similar to that observed for the addition of 2 equiv of chlorine to acetone in methanol.

The product distributions obtained from chlorination of acetone in methanol were substantially different from those obtained if the chlorination was conducted neat, in acetic acid, or in water.[6] In our hands, the chlorination

Scheme III



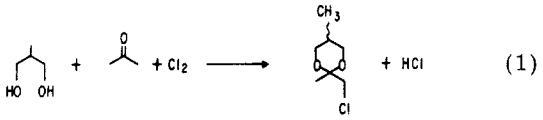
of acetone or a solution of acetone in acetic acid or carbon tetrachloride gave a 67:33 (1,1:1,3) mixture of dichloroacetones along with minor amounts of other products.[7]

The chlorination of acetone was further investigated, using ethanol, 2-propanol, 2,2-dimethyl-1-propanol, and a variety of diols as solvents. Chlorination of acetone or its diethyl ketal in ethanol gave results similar to the methanol chlorination. No significant change in the regiospecificity of chlorination was observed. However, the reaction was more exothermic and was accompanied by minor products not observed in chlorinations in methanol. Addition of small amounts of water had little effect on the specificity of chlorination in ethanol.

Attempted chlorination of acetone in 2-propanol resulted in oxidation of the solvent. The major reaction product was chloroacetone; both dichloroacetones were present as well as small amounts of other products.

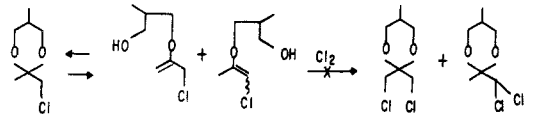
Chlorination of acetone in 2,2-dimethyl-1-propanol gives a complex mixture of products composed mainly (>85%) of chloro- and dichloroacetones, with 1,1-dichloroacetone predominating. Ketals or hemiketals, if present, are minor products.

Chlorination of acetone in ethylene glycol gives the cyclic ketal of chloroacetone as the only product. Even with excess chlorine no dichloro products are observed. The chloro ketal separates from the ethylene glycol solution and does not react further.[3] Chlorination of acetone or its 2-methyl-1,3-propylene ketal in 2-methyl-1,3-propanediol gives a mixture of cis and trans cyclic chloro ketals (eq 1).



(1)

Only minor amounts of dichlorinated products are observed even with excess chlorine. No phase separation occurs. Apparently after the first chlorination, intramolecular addition of the hydroxy group to the enol ether is faster than chlorination and no dichloro products are formed (eq 2).



(2)

Attempted chlorination of acetone in glycerol produced several products via oxidation of glycerol. Reaction of the glycerol ketal of acetone, solketal, in carbon tetrachloride resulted in separation of glycerol from the reaction mixture. Continued chlorination gave a normal mixture of dichloro ketones (67:33 1,1:1,3).

Chlorination of acetone in butanediol gave a mixture of ketals and ketones (Scheme III). The major product (28.3%) was the cyclic ketal of 1,3-dichloroacetone; the cyclic 1,1-dichloroacetone ketal was also present (13.8%). Large amounts of chloroacetone and 1,1-dichloroacetone were present. 1,3-Dichloroacetone, the cyclic ketal of chloroacetone and the 1,1,3-trichloroacetone cyclic ketal were minor products. The 1,3-dichloro ketal can be selectively crystallized from solution. Judging by ketal formation 1,3-chlorination predominates. However, if all dichlorinated products are taken into account, no selectivity is observed (29% 1,1-dichloro ketone, 21% 1,1-dichloro ketal, 7% 1,3-dichloro ketone, and 43% 1,3-dichloro ketal).

This result is typical of many chlorinations where both dichloro ketones and ketals are present in the reaction mixture. The 1,3-isomer tends to be present mainly as the ketal; the 1,1-isomer is present to a greater extent as the ketone. This reflects the greater ease in forming the 1,3-dichloro ketal vs. the 1,1-dichloro ketal. The amount of ketals vs. ketones present in the reaction mixture varies with the ketone structure and the amount of water present in the reaction mixture. When chlorinations were repeated, the ratio of ketals to ketones, as well as the ratio of chlorinated products, remained constant. A further problem in determining 1,1 vs. 1,3 selectivity in the chlorination of acetone is the high volatility of 1,1-dichloroacetone and the difficulty in separating it from chloroacetone. In all cases studied, care was taken to determine the accurate percentage of all chlorinated products present.

The bromination of a methanol solution of acetone was much slower than the chlorination. Unreacted bromine accumulated in the reaction flask, and excess bromine persisted long after halogen addition was complete. One hour after addition of bromine the solution was composed mainly of bromoacetone with small amounts of dibromoacetones. The ratio of 1,1- to 1,3-products was 32:68. After 24 h of being stirred at room temperature, the reaction mixture was composed mainly of dibromoacetone ketals. The overall ratio of 1,1- to 1,3-products was 26:74. The reaction yields were lower than the chlorinations, ~50%. 1,3-Dibromoacetone dimethyl ketal could be selectively crystallized from the crude reaction mixture.

Reaction of a basic water–methanol solution of acetone with 2 equiv of chlorine gave 1,1-dichloroacetone as the major product. No ketal or 1,3-dichloroacetone was formed. Chlorination of acetone in a 1:1 solution of methanol and dimethylformamide (DMF) gave a mixture in which 1,1-dichloroacetone was the major product (55%) with small amounts of 1,1,1-trichloroacetone (5%) and a mixture of 1,1- and 1,3-dichloroacetone dimethyl ketals, 18% and 22% (45:55). No 1,3-dichloroacetone was observed. Chlorination of acetone in DMF gave 1,1-dichloroacetone with small amounts of 1,1,1-trichloroacetone. No 1,3-dichloroacetone was observed.

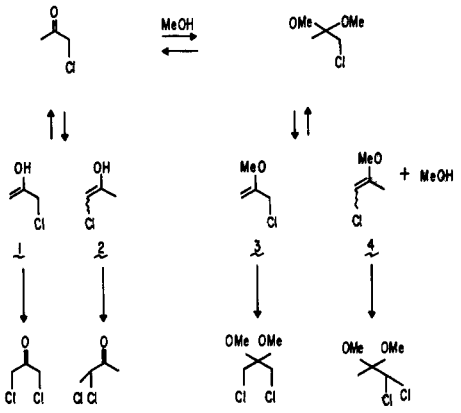
It appeared possible that the change in the regiospecificity of chlorination in methanol was a result of a change in the chlorinating species. In order to explore the mechanism of chlorination, several experiments were performed to determine the nature of the halogenating species.

The free-radical bromination of acetone using *N*-bromosuccinimide gives α,α-substitution.[8] We achieved similar selectivity using *N*-chlorosuccinimide in a photochemical addition. The crude product mixture was 95% 1,1-dichloroacetone with 5% 1,1,1-trichloroacetone. The chlorinating species is probably a chlorine radical although other reactions cannot be ruled out.

Solutions of *tert*-butyl hypochlorite in acetone showed no reaction after several hours at room temperature.

(6) C. Rappe, *Ark. Kemi*, **24**, 321 (1965).
(7) C. Rappe, *Acta Chem. Scand.*, **19**, 276 (1965).
(8) C. Rappe and R. Kumar, *Ark. Kemi*, **23**, 475 (1964).

Scheme IV



Addition of a trace of aqueous HCl accelerated the reaction; however, even with a large excess of hypochlorite only low conversions to chloroacetone were observed. A solution of *tert*-butyl hypochlorite and acetone in methanol was decolorized quickly at room temperature. Only a modest conversion to chloroacetone and chloroacetone dimethyl ketal was observed with a large excess of hypochlorite. Chloroacetone reacted with excess *tert*-butyl hypochlorite in carbon tetrachloride to give only 1,1-dichloroacetone in low yield. In a similar reaction the presence of methanol had no effect on selectivity.

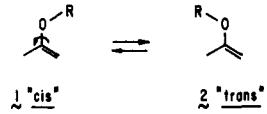
Free-radical chlorinations have the same regiospecificity as chlorination in base; the first chlorine directs the following chlorine to the same carbon. Since methanol can react with chlorine and accelerates the reactions of ketones with *tert*-butyl hypochlorite, it is tempting to invoke the intermediacy of methyl hypochlorite in chlorinations conducted in methanol. However, there is no evidence for involvement of this species in the reaction. A radical chlorination mechanism in methanol would enhance the formation of α,α-dichloro ketones. Experiments show that just the opposite occurs: α,α'-substitution is increased.

Discussion

In their study of the bromination of acetone in methanol, Toullec and Dubois conclude that even in the presence of small amounts of water the major reaction pathway involves bromination of enol ethers.[9] The mechanism is analogous to the halogenation of ketones where enol formation is the rate-determining step followed by rapid halogenation. It is reasonable to assume that the same mechanism is operating in the chlorination of ketones in methanol (Scheme IV). The distribution of products in a normal chlorination depends on the formation of enols 1 and 2. In methanol the isomer distribution is a function of the amount of enol ethers 3 and 4 formed.

The amount of each enol ether formed will reflect the relative stability of the various structures. It might be expected that the more substituted enol ether would be most stable and chlorination would proceed on the more substituted carbon. However, this is not the case; substitution at the less substituted α carbon is favored in methanol. Stability of the enol ethers appears to be dependent on steric effects.

The most stable configuration of enol ethers is assumed to be one in which the alkoxy group is coplanar to and eclipsed with the double bond.[3] As shown in eq 3, the "cis" configuration, 1, is favored over the "trans" configuration, 2. Since the most stable configuration of enol ethers places the alkyl group on oxygen "cis" to the double



(3)

bond, this creates increasing strain as substitution on the α carbon increases.

During chlorinations in methanol the formation of tetrasubstituted enol ethers is avoided and addition at an α carbon having two substituents is not favored. For example, in the chlorination of 3-methyl-2-butanone in methanol, addition at the 3-position is disfavored (8:92) since it would require formation of a tetrasubstituted enol ether.

Substitution of chlorine at a methyl or methylene position α to a carbonyl does not require the formation of a tetrasubstituted enol ether. Addition of chlorine at these positions is favored over substitution at a disubstituted α carbon. There is less selectivity observed in additions between a methyl or monosubstituted α carbon. The chlorination of 2-butanone in methanol only slightly favors the 1- vs. 3-position, 55:45.

The differences in the regiospecificity of chlorination in methanol vs. carbon tetrachloride (Scheme I) are all consistent with the formation and halogenation of the less hindered enol ether in methanol. Addition at a disubstituted α carbon is especially disfavored.

Chlorination of chloro ketones in methanol shows the same selectivity as observed in the chlorination of the parent ketones in methanol. The second chlorine is preferentially added to the less substituted α carbon. Chlorine is not efficient at stabilizing enol ethers.[10] Steric factors seem to be most important in determining the relative stability of the enol ethers derived from α-chloro ketones and the distribution of chlorination products. Addition of chlorine to a disubstituted α carbon is not favored since it requires formation of a tetrasubstituted enol ether.

The difference in reactivity between a methyl group and a monosubstituted α carbon is less than that of either vs. a disubstituted α carbon. The di- and trisubstituted enol ethers formed from a methyl-substituted and nonsubstituted α carbon are more stable than the tetrasubstituted enol ether resulting from reaction of a disubstituted α carbon. In the case of methyl vs. a monosubstituted α carbon, addition at the less substituted α carbon is still slightly favored. This preference is probably steric in origin. Chlorination of the ketone in carbon tetrachloride favors addition at the more substituted α carbon. The chlorination of chloroacetone in methanol shows a slight difference in selectivity between the methyl and chloromethyl positions. Addition to the less hindered methyl carbon is preferred, 60:40.

The chlorination of 3-chloro-4-heptanone clearly illustrates the effect methanol has on the position of chlorine attack. Chlorination in carbon tetrachloride shows little selectivity; presumably the two enols formed are of comparable stability. However, in methanol α,α'-dichloro products strongly predominate (93:7). Formation of α,α-dichloro products requires formation of a tetrasubstituted enol ether and is disfavored.

The products of the chlorination of 2-butanone in methanol are also consistent with the formation of the less substituted enol ethers. Addition of the first chlorine shows little perference for the 1- or 3-position, 55:45. In carbon tetrachloride, addition to the more substituted α carbon is favored (22:78). In methanol, addition of the second chlorine is more selective. The major products, 1,1-

(9) J. Toullec and J. E. Dubois, *J. Am. Chem. Soc.*, **98**, 5518 (1976).

(10) E. Tasdkinen and E. Sainio, *Tetrahedron*, **32**, 593 (1976).

and 1,3-dichloro ketones and ketals are derived from trisubstituted enol ethers. The products of the tetrasubstituted enol ether, 3,3-dichloro-2-butanone or its ketal, are not observed.

The importance of steric effects in determining the ratio of the chlorination products of ketones in methanol is again illustrated in the reaction of 3-methyl-2-butanone. Direct chlorination shows no selectivity; 1-chloro- and 3-chloro-2-butanones are formed in almost equal amounts (47:53). Chlorination in methanol is much more selective, giving 92% 1-chloro-2-butanone. This product is consistent with formation of the less hindered enol ether.

Addition of a second chlorine to a mixture of chloro-3-methyl-2-butanones in methanol shows very different selectivity vs. the same addition in carbon tetrachloride. Allowing for the fact that the 3-chloro-3-methyl-2-butanone initially formed by addition of the first chlorine can only yield 1,3-dichloro products, the addition of chlorine to 1-chloro-3-methyl-2-butanone is reversed in going from methanol to carbon tetrachloride. In methanol, addition at the 1-position is favored 84:16; in carbon tetrachloride addition at the 1- vs. 3-position is 26:74. Chlorination in methanol occurs at the least substituted position; formation of the hindered tetrasubstituted enol ether is avoided.

There was concern as to whether a kinetic or thermodynamic mixture of enol ethers was being formed under the reaction conditions and was responsible for the observed product distributions. While there is no definite proof, we feel a thermodynamic (or near thermodynamic) mixture is present. The chlorination of acetone in methanol or ethanol was repeated many times with variation in temperature and concentration with only marginal change in product distribution (<3%). Addition of HCl or $HClO_4$ at the beginning of the reaction had no effect on product distribution. In other cases, addition of $HClO_4$ has been useful in obtaining thermodynamic mixtures of enols. The 60:40 mixture of α,α'- to α,α-dichloro products formed in the chlorination of acetone is consistent with a study of the thermodynamic stability of halo enol ethers.[10] The pyrolysis of chloroacetone dimethyl ketal also supports this observation.[11]

In all chlorination reactions a small, but significant, amount of chlorinated products corresponding to the formation of the more sterically hindered enol ethers is also present. This is due to the fact that steric considerations are of importance but may not be the only factors determining product distribution. It must be kept in mind that the chlorination of enols is a minor competing pathway in all these reactions. If formation of an enol ether presents too much difficulty, the chlorination can always occur via the enol.

Summary

The chlorination of several ketones in methanol has been examined; the products differ substantially from those obtained by chlorination in carbon tetrachloride. Chlorination in methanol favors substitution at the least substituted carbon. The effect is especially pronounced if the ketone has two α substituents. The results are consistent with the formation and chlorination of the least hindered enol ether.

Experiments have shown that under the reaction conditions free-radical chlorination is unimportant. The reaction probably proceeds by an ionic chlorination of enol ethers.

(11) G. Greenwood and H. M. R. Hoffman, *J. Org. Chem.*, **37**, 611 (1972).

Experimental Section

General Procedures. Infrared spectra (IR) were taken on a Perkin-Elmer 457 grating spectrophotometer. Samples were dissolved in carbon tetrachloride. Nuclear magnetic resonance (NMR) spectra were taken on a Varian T-60, XL-100, or CFT-80 spectrometer. Samples were dissolved in chloroform-*d*, using tetramethylsilane as an internal standard. Gas chromatographic separations were performed on a Hewlett-Packard instrument (Model 5840A) equipped with a flame-ionization detector using an 8 ft × 0.25 in. stainless-steel column filled with 3% OV-17 on Chromosorb Q 60/80 mesh. Gas chromatographic mass spectral analyses (GC/MS) were obtained on a Varian MAT 111 system using a glass column with the same packing as described above.

Chlorination of Ketones in Methanol. All of the ketone chlorinations in methanol or other alcohols described in the text were conducted as described below.

Chlorine gas (1 or 2 equiv, 6.3–12.5 g) was condensed in a trap cooled in a dry ice–acetone bath. The trap was connected to a three-necked 250-mL flask fitted with a thermometer and reflux condenser. The flask contained a solution of 5.0 g of ketone in 150 mL of methanol. Chlorine was bubbled into the reaction mixture by allowing the trap to warm up slowly. The reaction temperature was controlled (20–50 °C) by using an ice bath and by regulating the rate of chlorine addition. Care must be taken to allow for an exotherm which often follows a brief induction period. This induction period, usually 5–10 min, may be shortened by addition of a catalytic amount of hydrogen chloride or by irradiation with a sunlamp.

In the experiments where ketones were allowed to react with 2 equiv of chlorine, cooling of the reaction was unnecessary after addition of the first equivalent of chlorine. A second equivalent of chlorine was introduced into the reaction mixture, keeping the temperature below 50 °C. Complete addition of 2 equiv of chlorine took ~1.5 h. After addition, the mixture was allowed to stand at room temperature for 0.5 h. The crude reaction mixture could be left for longer periods (~12 h) with no change.

The colorless crude reaction mixtures were worked up by extraction with 100-mL portions of water and methylene chloride. After separation the organic layer was washed with saturated aqueous sodium bicarbonate. There was no change in product distribution after either of these extractions. Hydrolysis of chloro and dichloro ketals is slow.[12] The organic layer was dried over anhydrous magnesium sulfate and analyzed by gas chromatographic mass spectral analysis before solvent was removed. Careful distillation of solvent gives the mixture of chlorination products in good yield 80–100%.

The relative amounts of products from the reaction mixtures are shown in Table I. These values were determined by gas chromatographic analysis of the reaction mixtures which had been extracted with water and are uncorrected for relative detector response. Assignment of peaks in the gas chromatograph traces was made by analysis of the mass spectra of each compound. Structures were assigned on the basis of the fragmentation patterns of the various α-chloro ketones and ketals present, many of which have been reported in the literature.[13] In the cases of acetone and 3-methyl-2-butanone, reaction mixture compositions were also determined by integration of the NMR spectrum of the crude reaction mixture and were in good agreement with gas chromatographic results. In some cases, coinjection of the reaction mixtures with authentic samples of ketal or ketone was also used to confirm assignment of peaks.

The chlorination of acetone in alcohols was examined in detail. The addition of a small amount of aqueous or anhydrous HCl at the start of the reaction shortened the induction period but caused no change in the final product distribution. Likewise, addition of 1% water had no substantial effect on the reaction. Chlorination in anhydrous methanol gave the same results as observed in other reactions.

Analysis of the reaction mixture by fractional distillation of the crude reaction products gave results identical with the gas

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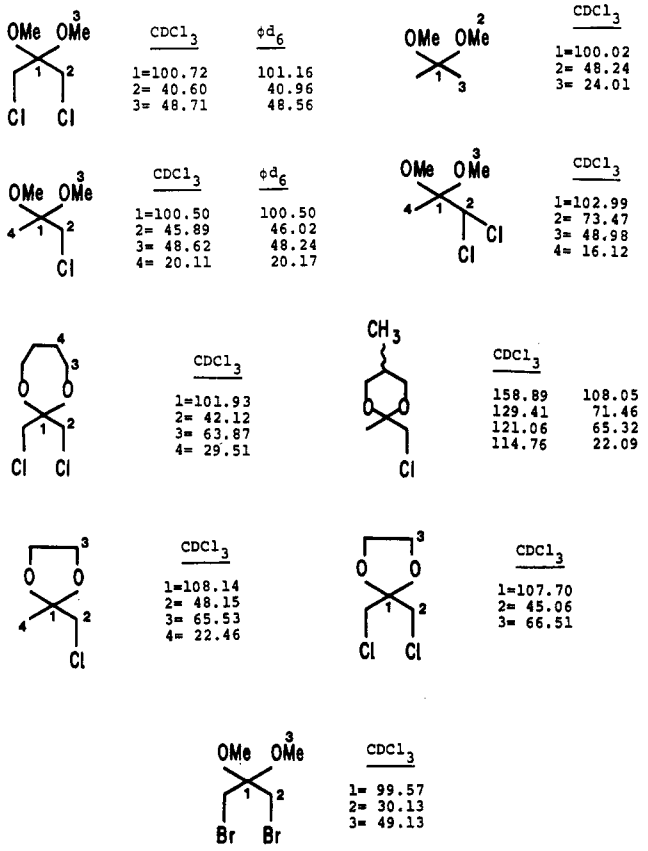
Table II. ^{13}C NMR Chemical Shifts



chromatographic analysis. The α,α-dichloro ketal or the α,α'-dichloro ketal was uneffected by reaction with acidic methanol. Short contact (~15 min) with aqueous HCl at room temperature also resulted in no reaction. Chloroacetone, 1,1-dichloroacetone, 1,3-dichloroacetone, and their corresponding ketals are not retained in the aqueous phase of an extraction using equal volumes of methylene chloride and water. Cooling of the reaction mixtures, obtained by allowing acetone to react with 2 equiv of chlorine in methanol or 1,4-butanediol solution, to 0 °C resulted in crystallization of the α,α'-dichloro ketal.

Chlorination of acetone in ethanol gave results very similar to those observed for the chlorination in methanol: 1,1-dichloroacetone diethyl and 1,3-dichloroacetone diethyl ketals were the only products present in a 60:40 ratio.

Chlorinations of the methyl ketal of acetone in methanol or the ethyl ketal in ethanol were conducted as described above. The product mixtures were identical with those formed in the chlorination of acetone in the corresponding alcohol.

The preparation and properties of most of the compounds prepared in these reactions are contained in the references cited. The properties and spectra of new compounds are listed below. ^{13}C NMR spectral data of various ketals are summarized in Table II.

2,2-Bis(chloromethyl)-1,3-dioxacycloheptane: IR (CCl_4) 2950, 1470, 1435, 1305, 1220, 1115, 1065 cm^{-1}; NMR ($CDCl_3$) 3.7–4.0 (m, 4 H), 3.7 (s, 4 H), 1.9–1.6 (m, 4 H); mp 88–90 °C (EtOH).

cis- and *trans*-2-(chloromethyl)-2,5-dimethyl-1,3-dioxacyclohexane: IR (CCl_4) 2960, 2850, 1455, 1385, 1240, 1115, 1048, 905 cm^{-1}; NMR ($CDCl_3$) 3.9–3.2 (m 6 H), 2.2–1.6 (m, 1 H), 1.5–1.3 (2 s, 3 H), 1.0–0.7 (2 d, 3 H); bp 33–37 °C (0.05 mmHg).

Chlorination of Ketones in Carbon Tetrachloride. The chlorination of ketones in carbon tetrachloride solution was conducted in a manner similar to the chlorinations run in methanol. Chlorine (6.3–12.5 g) was condensed in a dry ice–acetone trap and bubbled into a solution of 5.0 g of ketone in 150 mL of carbon tetrachloride. Care was taken to keep the temperature of the reaction below 40 °C. At higher temperatures, further reactions of the chloro ketones were observed. After addition of the chlorine (~1.5 h) the reactions were allowed to stir at room temperature for 0.5 h. The reactions were worked up by extraction with water followed by extraction with saturated aqueous sodium bicarbonate. The organic layer was dried over anhydrous magnesium sulfate and analyzed by GC/MS.

It is important to workup the reactions quickly since some reaction mixtures, especially those using 2 equiv of chlorine, slowly decompose. In order to determine if product interconversion took place under the reaction conditions, the mixtures were allowed to stand after the end of chlorine addition. The reaction composition was monitored by gas chromatography. With internal standards, the disappearance of products was observed. The overall rate of reaction was slow, and while the rates at which the various compounds reacted were different, no peak was observed to increase in size relative to the standard. In all chlorinations, the product distributions observed early in the reaction are similar to the composition of the final mixture of products.

Sealed tubes (screw caps) of carbon tetrachloride and 1,3-dichloro- or 1,1-dichloroacetone (0.25 g/3 mL) were allowed to react with a variety of acids at 25 and 50 °C. With catalytic amounts of anhydrous HCl, anhydrous HBr, $FeCl_3$, or $AlCl_3$, no interconversion of dichloroacetones was observed. Similar reactions using glacial acetic acid as solvent also gave no interconversion. In all cases, decomposition to higher molecular weight products predominated.

Bromination of Acetone in Methanol. Bromine (27.6 g) was added dropwise to a solution of acetone (5.0 g) in methanol (100 mL). Initially the reaction was rapidly decolorized but then slowly turned dark red-brown. A sample was worked up 1 h after bromine addition by adding the reaction mixture to an aqueous solution of sodium bisulfite, then extracting with methylene chloride, and washing the organic layer with water. After the solution was dried over anhydrous magnesium sulfate, gas chromatographic analysis showed bromoacetone (38.9%), 1,1-dibromoacetone (13.4%), 1,3-dibromoacetone (28.1%), and both the 1,1- and 1,3-dibromo ketals (4.2% and 9.4%). 1,3-Dibromo products predominated (1,3 vs. 1,1, 68:32).

After being stirred for 24 h the reaction mixture contained almost no free ketone (9.2% 1,1 and 2.6% 1,3). 1,3-Dibromoacetone dimethyl ketal was the major product (64%) with 24% 1,1-dibromo ketal and 15% 1,1,2-tribromoacetone dimethyl ketal. Cooling of the crude reaction mixture to 0 °C resulted in crystallization of the dimethyl ketal of 1,3-dibromoacetone.

Chlorination of Acetone in DMF. Acetone, 6.2 g, was dissolved in 50 mL of DMF and allowed to react with 17.0 g of chlorine (~10% excess) which was bubbled into the reaction mixture from a trap cooled in a dry ice–acetone bath. The reaction mixture was cooled in an ice bath. The temperature was kept below 50 °C. Chlorine addition took ~2.0 h. The major product, 1,1-dichloroacetone, could be distilled directly from the crude reaction mixture, yield 17.9 g (64%).

Alternatively the reaction could be worked up by extraction with 50 mL of carbon tetrachloride and 100 mL of 2 N HCl. The organic phase was washed two additional times with water and dried over anhydrous magnesium sulfate. Gas chromatographic mass spectral analysis showed only two products, 1,1-dichloroacetone and 1,1,1-trichloroacetone (95:5).

Reaction of Acetone or Chloroacetone with *tert*-Butyl Hypochlorite. Acetone (0.5 g) was dissolved in 10 mL of carbon tetrachloride and stirred in a capped vial at room temperature with 3.0 g of *tert*-butyl hypochlorite. The reaction was monitored by NMR spectroscopy and gas chromatography; only traces of chloroacetone were present after 24 h. A similar reaction using methanol as solvent was rapidly decolorized, giving small amounts of chloroacetone and its dimethyl ketal after 1 h. Addition of a trace of acid or methanol to the reaction in carbon tetrachloride greatly increased the rate of reaction, but no dichloro products were found.

In similar reactions, carbon tetrachloride or methanol solutions of distilled chloroacetone gave small amounts of 1,1-dichloroacetone (accompanied by its ketal in methanol). No 1,3-dichloro products were observed.

Reaction of *N*-Chlorosuccinimide with Acetone. The reaction was conducted as in ref 8, using *N*-chlorosuccinimide. A carbon tetrachloride solution of acetone and *N*-chlorosuccinimide was irradiated at 50 °C for 24 h, using a General Electric sunlamp. The reaction mixture was filtered, washed with water, and dried over anhydrous magnesium sulfate. The products could

be isolated by vacuum distillation. Analysis of the crude reaction mixture by gas chromatography and NMR spectroscopy showed 95% 1,1-dichloroacetone and 5% 1,1,1-trichloroacetone.

Acknowledgment. We thank P. Donahue for recording ^{13}C NMR spectra and R. May and H. Grade for the many gas chromatographic mass spectral analyses. Helpful discussions with G. Davis, G. Faler, and J. Verbicky are also greatly appreciated.

Registry No. 1,1-Dichloro-2,2-dimethoxypropane, 32730-70-4; 1,1-dichloroacetone, 513-88-2; 1,3-dichloro-2,2-dimethoxypropane, 6626-57-9; 1,3-dichloro-2-propanone, 534-07-6; 5,5-dichloro-4-heptanone, 77416-00-3; 3,5-dichloro-4-heptanone, 77416-01-4; 3,5-dichloro-4,4-dimethoxyheptane, 77416-02-5; 1-chloro-2-butanone, 616-27-3; 1-chloro-2,2-dimethoxybutane, 77416-03-6; 3-chloro-2-butanone, 4091-39-8; 2-chloro-3,3-dimethoxybutane, 77416-04-7; 1,3-dichloro-2-butanone, 16714-77-5; 1,3-dichloro-2,2-dimethoxybutane, 77416-05-8; 3-chloro-3-methyl-2-butanone, 5950-19-6; 1-chloro-3-methyl-2-butanone, 17687-63-7; 1,1-dichloro-3-methyl-2-butanone, 39140-45-9; 1,1-dichloro-2,2-dimethoxy-3-methylbutane, 77416-06-9; 1,3-dichloro-3-methyl-2-butanone, 57539-84-1; 1,3-dichloro-2,2-dimethoxy-3-methylbutane, 77416-07-0; bromoacetone, 598-31-2; 1,1-dibromoacetone, 867-54-9; 1,3-dibromoacetone, 816-39-7; 1,1-dibromoacetone dimethyl ketal, 77416-08-1; 1,3-dibromoacetone dimethyl ketal, 22094-18-4; 1,1,3-tribromoacetone dimethyl ketal, 77416-09-2; 1,1,1-trichloroacetone, 918-00-3; 2,2-dimethoxypropane, 77-76-9; 1,1-dichloro-2,2-dimethoxypropane, 2718-42-5; 2,2-bis(chloromethyl)-1,3-dioxacycloheptane, 77416-10-5; *cis*-2-(chloromethyl)-2,5-dimethyl-1,3-dioxacyclohexane, 77416-11-6; *trans*-2-(chloromethyl)-2,5-dimethyl-1,3-dioxacyclohexane, 69245-13-2; 2-methyl-2-chloromethyl-1,3-dioxacyclopentane, 4469-49-2; 2,2-bis(chloromethyl)-1,3-dioxacyclopentane, 26271-50-1; acetone, 67-64-1; 2-butanone, 78-93-3; 3-methyl-2-butanone, 563-80-4; 4-heptanone, 123-19-3.

Supplementary Material Available: Mass spectral data of α-chloro ketones and ketals (4 pages). Ordering information is given on any current masthead page.

Enantiomeric Interactions and Reaction Rates: Ketalization of (*S*)- and (*RS*)-1,2-Propanediols

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Aliphatic ketones, e.g., butanone, are converted nearly quantitatively to the corresponding dioxolanes (ketals) in neat (*S*)- or (*RS*)-1,2-propanediol containing dichloroacetic acid. The reactions follow the pseudo-first-order law at a given acid concentration, are inhibited by water, and proceed approximately twofold faster in (*RS*)-diol-*O*,*O*-d_2 than in undeuterated diol. No difference in rates greater than 1% could be detected between (*S*)- and (*RS*)-diols at identical temperatures, acid concentrations, and water concentrations. Thus, for a chiral diol molecule and the activated complex, free-energy differences are virtually the same in (*S*)- and (*RS*)-diols as solvents. Differences in interactions among identical and enantiomeric molecules, if any, are evidently matched by differences in the activated complexes.

Various reports over the years have called attention to differences in properties between chiral compounds and the corresponding racemic compounds,[2] e.g., tartaric acid[3] and hydrobenzoin.[4] The dramatic differences in melting points and solubilities probably originate largely from strong interactions in the solid state.

More subtle, however, is the question whether pure enantiomers behave differently from their racemates *in solution*. The environment of a given chiral molecule, denoted *R*, in a sample of neat liquid *R*, will be diastereomeric with and thus different from that in neat liquid racemic mixture, *RS*. Since all real substances behave nonideally to some extent, the possibility of at least slight differences in behavior at high concentrations must be taken seriously.

Horeau has critically reviewed the available evidence concerning physical properties[5] and concluded that diastereomeric interactions between enantiomers in solution can give rise to measurable free-energy differences.

Recent reports from these laboratories[6] have discussed what are apparently the first observations of differences in *chemical reactivity*. Since the sum total of chemical entities in eq 1 and 2 are neither identical nor enantiomeric, they must be diastereomeric. Free-energy differences between the ground states and/or between the transition states could in principle lead to differences in activation energies. Evidence for such differences was manifest in differences in stereoselectivities of two coupling reactions and a ketone reduction.[6a] These differences were interpreted in terms of two effects: (1) enantiomeric recognition, the preferential reaction of a molecule with either an identical molecule or its antipode, as the case might be; (2) antipodal interaction, essentially differential solvation of a reacting molecule, which is the effect of interest in the present investigation.

$$R \text{ isomer} \xrightarrow{\text{reagent}} \text{products} \quad (1)$$

$$RS \text{ mixture} \xrightarrow{\text{reagent}} \text{products} \quad (2)$$

(1) To whom correspondence should be addressed at Filson Chemical Laboratories. This paper is based on work performed during this author's sabbatical leave at Groningen, 1977-1978.

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